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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/309,038	05/10/1999	PETER BERNARD HEIFETZ	A-30496B	7012

22847 7590 06/07/2005

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EXAMINER	
MEHTA, ASHWIN D	
ART UNIT	**PAPER NUMBER**
1638	

DATE MAILED: 06/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/309,038	HEIFETZ ET AL.	
	Examiner	Art Unit	
	Ashwin Mehta	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12,16-30,34-40,49,56,58,73 and 76-89* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12,16-30,34-40,49,56,58,73 and 76-89* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application on October 15, 2004, after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's claim amendments, submitted September 8, 2004 have been entered.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. The rejection of claims 47, 49, 56, 58, and 86 under 35 U.S.C. 112, 2nd paragraph, are withdrawn in light of the claim amendments or cancellations.

Specification

4. The specification recites co-pending U.S. patent application numbers on pages 13 and 18. Applicants should amend the citations to indicate the status of those applications: 'now abandoned' or, if allowed and issued, the patent number.

Claim Rejections - 35 USC § 112

5. Claims 12, 16-30, 34-40, 49, 56, 58, 73, 62, 73, and 76-89 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reasons of record stated in the previous Office actions.

Applicants argue that the nucleotide sequence of BNYVV RNAI was available, that it was published in 1987 in GenBank Acc. No. D00115 and revised in April 1998, the updated 1998 version being provided in Exhibits 1-3 (response filed September 8, 2004, page 8, 2nd full paragraph). However, that "a" version of this sequence was available at the time of tiling is not the issue. The sequence at this GenBank accession number was replaced after the filing date of the instant application, in February 2002. Applicants have admitted this in the response filed February 11, 2004, on page 9. The specification cannot be said to describe something that was unknown at the time of filing. Applicants also argue that claim 82 was amended to recite a sequence identifier (response, page 8, 3rd full paragraph). However, claim 82 does not recite any sequence identifier.

Regarding the lower size limit of the fragments of RNA that can be used in the claimed invention, the claims have been amended to recite that the fragments are at least 15 nucleotides in length. However, the specification does not teach any 15 nucleotide long fragment that confers virus resistance when expressed in both orientations in a plant cell. The smallest size fragment that Applicants describe that conferred increased resistance viral resistance (to BNYVVI in plants is a 452 nucleotide fragment consisting of nucleotides 5168 to 5620 BNYVV

RNAI (Example 9; declaration submitted 19 June 2001). The specification does not describe any viral genome portions smaller 452 nucleotides that conferred viral resistance to plant cells with the claimed method. Voinnet (Trends in Genetics, 2001, Vol. 17, pages 449-459) teaches that 21-23 nt. long RNAs are formed from the targeted transcript during RNA silencing in virus-infected plant cells (page 451). The specification has not described any viral genome portions smaller than 21 nucleotides that can be used with the claimed invention, as encompassed by the claims.

Further, the amended claims now indicate that resistance or tolerance is conferred to more than one virus selected from the group consisting of any furovirus, any potyvirus, any tospovirus, and any cucomovirus. However, the specification does not describe any such sequence that confers resistance or tolerance to more than one of the recited viruses. No information is provided at all regarding the sequences of any of the recited viruses that, when used with the claimed method, will confer resistance or tolerance to more than one virus with which it does not share homology at the nucleotide sequence level. Furthermore, page 18, 1st full paragraph, of the specification indicates that when the method leads to resistance or tolerance to a broad spectrum of viruses, the other viruses are in the same class, group, genus, species, or are different isolates of the same virus, from which the first and second DNA sequences are from. The amended claims, however, broadly encompass conferring resistance or tolerance to multiple viruses from that do not belong to the same class. This embodiment is NEW MATTER and must be removed from the claims.

6. Claim 81 remains rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not

described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reasons of record stated in the previous Office actions.

The amended claim now recites that the portion of the BNYVV replicase gene is 452 nucleotides. Applicants indicate that support is found on page 42, lines 26-27 (response, page 7). This portion of the specification indicates that a PCR product has the sequence of nucleotides 5168-5620 of BNYVV RNAI. While this fragment consists of 452 nucleotides, the claim broadly encompasses any other 452 nucleotide fragment besides this one. Written descriptive support is lacking for other 452 nucleotide fragments from the BNYVV replicase gene. This recitation is NEW MATTER and must be removed from the claim.

7. Claims 12, 16-30, 34-40, 49, 56, 58, 73, 76-89 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for the reasons of record stated in the previous Office actions.

Regarding the issue of the BNYVV sequences recited in claim 82, Applicants have amended the claim to recite Genbank Accession No. D00115. However, as discussed above, the sequence of this Genbank entry was revised after the filing of the instant application. These sequences were therefore not enabled at the time of filing.

Regarding the issue concerning the enablement of the portion of the viral RNA fragments that can be used with the invention, the have been amended to recite that RNA fragments are at

least 15 nucleotides in length (response, page 10, 6th full paragraph). However, Applicants admit, in Exhibit 3 (last page, submitted with the declaration submitted February 11, 2004), that the smallest fragment sufficient for resistance is 150 nucleotides. Applicants have not enabled the claimed invention using portions of viral genomes as small as 15 nucleotides. In light of Applicants' admittance, undue experimentation would be required by one skilled in the art to make and use RNA fragments as small as 15 nucleotides in length to confer resistance to plants against a furovirus, potyvirus, tospovirus, or cucomovirus, or to more than one of those viruses. Further, the specification does not teach any RNA fragments from the viruses recited in the claims wherein the same fragments can confer resistance or tolerance to the other viruses. The specification even teaches that when the method leads to resistance or tolerance to a broad spectrum of viruses, the other viruses are in the same class or group as that from which the RNA fragments came from (page 18). In the absence of further guidance and in light of the teachings of the specification, undue experimentation would be required by one skill in the art to express a first DNA sequence encoding a sense RNA fragment and a second DNA sequence encoding a antisense fragment, wherein the two fragments form a double-stranded RNA molecule and this same double-stranded molecule confers resistance or tolerance to to a plant cell against more than one of a furovirus, potyvirus, tospovirus, and a cucomovirus. See Genentech, Inc. v. Novo Nordisk, A/S, 42 USPQ2d 1001, 1005 (Fed. Cir. 1997), which teaches that "the specification, not the knowledge of one skilled in the art" must supply the enabling aspects of the invention. Given the breadth of the claims, unpredictability of the art and lack of guidance of the specification as discussed above, undue experimentation would be required by one skilled in the art to make and use the claimed invention.

Claim Rejections - 35 USC § 103

7. Claims 12, 16-30, 34-40, 49, 56, 58, 73, 76-80, and 83-89 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fire et al. (U.S. Patent No. 6,506,559) in combination with de Haan et al. (J. Gen. Virol., 1991, Vol. 71, pages 2207-2216), Maiss et al. (J. Gen. Virol., 1989, Vol. 70, pages 513-524), Saito et al. (Arch. Virol., 1996, Vol. 141, pages 2163-2175), Hsu et al. (Arch. Virol., 1995, Vol. 140, pages 1841-1847), Miki et al. (Procedures for Introducing Foreign DNA into Plants, In Methods in Plant Molecular Biology and Biotechnology, 1993, Bernard R. Glick and John E. Thompson, Eds., CRC Press, Inc., Boca Raton, FL), Baulcombe, D.C. (Plant Cell, 1996, Vol. 8, pages 1833-1844), Applicants' admitted state of the prior art, and Keddie et al. (Plant Mol. Biol., 1994, Vol. 24, pages 327-340).

The claims are broadly drawn towards a method for conferring resistance or tolerance to more than one virus selected from the group consisting of furovirus, potyvirus, tospovirus, or cucomovirus upon any plant cell, comprising introducing into a plant cell a first DNA sequence encoding a sense RNA fragment of the genome of portion thereof of one of said viruses, and a second DNA sequence encoding an antisense RNA fragment of said viral genome or portion thereof, wherein said fragments form a double-stranded molecule when expression in a plant cell, wherein the fragments of RNA are at least 15 nucleotides in length and wherein the expression of said viral genomes or portions thereof in said cell is reduced; or wherein the RNA fragments are in two different molecules, or mixed before introduction into the cell, or introduced sequentially into the cell, or are comprised in the same RNA molecule; or said

method wherein the RNA fragments are expressed from DNA; a plant cell obtained from said method; a plant obtained from said cell; seed derived from said plant.

Fire et al. teach a method to inhibit expression of a target gene in a cell comprising formation of a double-stranded RNA in a cell, wherein one strand of the RNA corresponds to a nucleotide sequence found within a target gene and wherein the second strand is complementary to the first strand, and the double stranded RNA inhibits expression of the target gene. The cell types comprising the target gene include plant cells. The target gene may be a gene from a pathogen that is capable of infecting the cell, including viruses. A single, self-complementary RNA, or two complementary RNA strands may form the double-stranded RNA. RNA duplex formation may be initiated either inside or outside the cell. The RNA strands may also be transcribed inside the cell from transgenes comprising regulatory regions, which include promoters and splice donor and acceptors. The lengths of the RNA fragments that can be used include those that are 400 bases (col. 4, line 20 to col. 5, line 3; col. 6, lines 44-49; col. 8, lines 4-5; col. 10, lines 8-9; col. 11, lines 37-40; claims).

Fire et al. do not teach plant virus sequences, or tissue-specific, developmentally regulated, inducible, or bi-directional promoters.

de Haan et al. teach nucleotide sequence of the L RNA of the tomato spotted wilt virus (TSWV), and assert that this virus is a member of the tospovirus genus of the Bunyaviradae, which infect plants (pages 2207-2211, 2215).

Maiss et al. teach the nucleotide sequence of the plum pox virus (PPV), a member of the potyvirus group, and assert that it causes heavy yield losses in plum, peach, and apricot (pages 513, 515-523).

Saito et al. teach the nucleotide sequence of the Japanese isolate S of beet necrotic yellow vein virus (BNYVV), and assert that this virus is responsible for rhizomania disease of sugar beet, and that RNA1 encodes functions required for viral RNA replication (page 2163, 2165-2173).

Hsu et al. teach the nucleotide sequence of the cucumber mosaic virus (CMV) and assert that it is one of the most widespread plant viruses infecting 775 plant species, including both monocots and dicots (pages 1841-1846).

Miki et al. teach Agrobacterium- and microprojectile-mediated methods to stably transform plants (pages 67-83).

Baulcombe teaches that since post-transcriptional gene silencing operates at the RNA level that viral RNA that shares sequence identity with a silenced target would also be suppressed (pages 1834-1835).

Applicant's specification admits that the prior art teaches plant tissue specific, developmentally regulated and inducible promoters, use of intron sequences, and methods to introduce RNA into plant cells (pages 13, 20-22).

Keddie et al. teach a plant bi-directional promoter (pages 332-338). This reference is cited to address the limitation of bi-directional promoters.

It would have been obvious and within the scope of one of ordinary skill in the art at the time the invention was made to use the method of inhibiting expression of a target gene of Fire et al. to introduce into plant cells, a sense RNA fragment of a plant virus, and its complementary sequence, or DNA encoding said RNA, such that the two RNA fragments form a double stranded RNA molecule in the cell, and inhibit expression of a gene expressed by the virus, when that

virus infects the cell. It would have been obvious that such inhibition would have increased the resistance or tolerance of the plant cell to that plant virus. It would have been obvious to stably transform a plant cell with a DNA construct that comprises DNA sequences encoding sense and antisense RNA fragments from a viral gene of any plant virus, including a fragment from the TSWV, PPV, BNYVV, and CMV genomes, taught by de Haan et al., Maiss et al., Saito et al., and Hsu et al., respectively, operably linking the nucleotide fragments to promoters such that sense- and anti-sense RNA fragments get expressed and form a dsRNA molecule. Any appropriate plant transformation method could have been used, including those taught by Miki et al. It was obvious that the RNA fragment could have been from viral genes required for infection, such as genes required for viral RNA replication. As Saito et al. assert, BNYVV RNA1 contains sequences needed for viral replication. It would have been obvious to use any portion of this gene, including sequences from the 3' end. As taught by Fire et al., the dsRNA inhibits expression of the target gene from which the sequences were taken. Fire et al. teach that a single, self-complementary RNA, or two complementary RNA strands could have formed the double-stranded RNA. Therefore it was obvious that the two sequences could have been encoded by the same strand of DNA in the DNA construct, or on complementary strands, or on different DNA constructs that get co-transformed into the cell. The claims indicate that resistance or tolerance is conferred to more than one virus from the group consisting of furovirus, potyvirus, tospovirus, or cucomovirus. This can be interpreted to mean different isolates of tospovirus, if the RNA fragments were derived from a tospovirus, for example. It was obvious that resistance or tolerance would also be conferred against other viruses that comprise a sequence that shares homology with the target sequence. It was also obvious that the sense- and

anti-sense-encoding DNA sequences could have been operably linked to any of a variety of different constitutive, developmentally-regulated, inducible, or tissue-specific promoters, depending on one's desired end. These promoters were taught in the art, as admitted in Applicants' specification. One could also have used a bi-directional promoter, such as that taught by Keddie et al. Whether the two promoters regulating the two sequences were of the same type or different was a matter of choice. The sense-and anti-sense encoding DNA sequences could also have been operably linked to the same promoter and been transcribed into a single RNA molecule, in which case a linker sequence obviously would have been placed in between the two sequences so that steric hindrance would not have prevented the expressed RNA from forming a double-stranded molecule. The linker sequence could also have included an intron, such as that taught by Applicants' admitted state of the prior art. It would also have been obvious to collect seed from the transgenic plants for the purpose of propagation, to produce progeny that have inherited the DNA encoding the RNA fragments, thereby inheriting the viral resistance or tolerance. The sense- and anti-sense RNA fragments themselves could also have been introduced into cells of a plant directly, as taught by Fire et al. Many obvious variations on this theme would also have worked, as long as the sense- and anti-sense RNA sequences of the target gene were present so that they formed a dsRNA molecule in the plant cell. That is, the sense- and anti-sense RNA sequences could also have been on the same molecule, on two different RNA molecules, mixed before introduction into the cell, or introduced sequentially, since the important aspect is dsRNA formation. One would have been motivated to prevent replication of these viruses in plant cells and plants, given that they were known plant pathogens.

8. All pending claims remain rejected.

Contact Information

Any inquiry concerning this or earlier communications from the Examiner should be directed to Ashwin Mehta, whose telephone number is 571-272-0803. The Examiner can normally be reached from 8:00 A.M to 5:30 P.M. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Amy Nelson, can be reached at 571-272-0804. The fax phone numbers for the organization where this application or proceeding is assigned are 571-273-8300. Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov.

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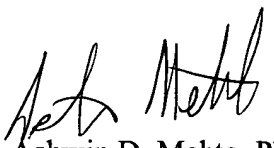

May 27, 2005

Ashwin D. Mehta, Ph.D.
Primary Examiner
Art Unit 1638